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The principal purpose of this trial is to assess the potential for the essential nutrient **selenium** (Se) to modulate biomarkers of prostate cancer between initial diagnostic biopsy and radical prostatectomy. The scope of work is to randomize at least 110 participants to either a placebo or Se dosages of 200 μg, or 400 μg/day. Recruitment is continuing as a result of a one-year no-cost extension. A total of 69 subjects have been randomized. Of these, 59 have completed the study, 5 dropped before completing the study, and 5 are in the process of completing the study.

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Table of Contents

INTRODUCTION

The principal purpose of this trial is to assess the potential for the essential nutrient selenium (Se) to modulate biomarkers of prostate cancer. The rationale for this trial is based on the results of the Nutritional Prevention of Cancer (NPC) Trial. In that study, a double-blind, randomized clinical trial, a 63% reduction in prostate cancer incidence was observed during the initial 10 years of follow-up in participants receiving 200 μg of Se compared to those receiving a placebo (JAMA 276:1957-63 (1996)). Objective: The primary endpoint for this trial consists of changes in biomarkers between tissues obtained at the initial diagnostic biopsy and radical prostatectomy. Relevance: This study has the potential to provide direct evidence for the activity of selenium in prostate tissue. Methods: A study population of prostate cancer subjects scheduled for prostatecomy was selected so that prostate tissue can be examined for biomarker changes before and after supplementation with selenium. This trial will randomize participants to either a placebo or one of two Se dosages: 200 μg, or 400 μg/day. The trial will randomize at least 110 patients, in order to have 80% power to detect an effect size of 0.66 standard deviations. Progress: A total of 69 subjects have been randomized. Of these, 59 have completed the study, 5 dropped before completing the study, and 5 are in the process of completing the study.

PROGRESS

Task 1: Training and Preparation for Trial (Months - Ongoing)

- A database has been created for this study and staff at the Tucson Coordinating Center (TCC) have been trained in its use. Routine reports are available to assist staff in tracking subjects from initial referral through randomization.
- Staff at TCC and study sites have been trained to explain the study requirements to subjects and to inquire about adverse effects. TCC laboratory staff have established routines to ensure that the proper blood kits for the various tests performed after each visit are used.
- Randomization codes have been prepared and appropriate staff have been blinded to blood tests results that might reveal the subject's treatment.
- Pills are dispensed according to randomization codes by staff blinded to treatment status.
- An "Initial Questionnaire", "Follow-up Study Visit" questionnaire, and "Urological Symptoms Questionnaire" have been developed. A food frequency questionnaire developed by the Fred Hutchinson Cancer Center in 1992 is also being administered to study subjects.
- All appropriate laboratory materials to obtain, handle, store, and prepare blood and tissue samples for analyses have been obtained.
- Training has been ongoing as new sites are added to the study.

Task 2: Subject Recruitment, Enrollment (Months 3-34)

Recruitment for this study has been slow despite frequent contact with physician offices. It now appears that participating physicians overestimated the number of eligible patients they can provide. In addition, we initially imposed a recruitment requirement for frozen tissue that led many urologists to withdraw from the study. Since we eliminated this requirement, we have been able to reestablish participation from many of the urologists who originally agreed to refer patients. Still, actual referrals have been far lower than original estimates. Further, only 55 percent of those referred by physician offices have been randomized. Factors which have contributed to the slow pace of recruitment include:

- *Time for Patient Recruitment.* The window of opportunity for enrolling subjects to this study – the three to six week period between diagnosis and surgery – limits the type of recruitment methods available. These subjects must be identified as soon as possible after diagnosis during a time when they are struggling with the emotional impact of their diagnosis. Advertisements and health fairs, which have yielded some subjects for our other selenium and prostate cancer studies, have been ineffective for this study.
- *Inadequate Number of Referring Physicians.* During the early stages of the study, the primary focus was on Tucson urologists. Dr. Bruce Dalkin, the Co-Principal Investigator, has been the greatest source of subjects for this study. During the last year, urologists at remote sites: Dr. Martha Terris at the Palo Alto VA in Palo Alto, CA, and Dr. Christopher Julian at the Urological Associates of Central California in Fresno, CA have made significant contributions to this study. Additional remote sites have received initial IRB approval and will be submitted to HSRRB for approval as follows:
    - Dr. Dennis Venable at Louisiana State University in Shreveport, LA
    - Dr. Graham Greene at the Arkansas Cancer Research Center, Little Rock, AR
    - Dr. Anthony Smith at the University of New Mexico in Albuquerque, NM
    - Roswell Park Cancer Institute in Buffalo, NY

  In addition, the University of Arizona Cancer Center has recently established a clinic in Scottsdale overseen by Dr. Michael Gordon and subjects are now being recruited from the entire Phoenix area.

  Also, our collaborating urologists in New Zealand have expressed interest in enrolling subjects. They are in the process of initial Ethics Committee review and will be submitted to HSRRB for approval.
- *Protocol Changes.* Protocol changes were made in March and July 2000. The first change eliminated the requirement for frozen tissue samples and appears to have had a positive effect on recruitment. The protocol changes made in July 2000 significantly slowed the rate of physician referrals due to delays in securing IRB approval for these complex changes. These changes eliminated the follow-up portion of this study and made the changes in tissue biomarkers the primary endpoint. These changes have been approved by HSRRB.
- *Documentation requested by HSRRB.* Due to the various IRB submissions and due to delays including events related to September 11, we have not been allowed to open new sites which would have accelerated recruitment. Approvals have now been granted by HSRRB for our main sites and we are in the process of submitting the required documents for new sites.

Of the 69 randomized subjects, there are 2 Hispanics, 1 African American, 1 Asian and 65 Caucasian. However, LSU serves a largely minority population and our discussions with the Arkansas Cancer Research Center lead us to hope for better recruitment from the African-American population there.

Task 3: Baseline Data Collection (Months 3-34)

At time of enrollment, all participants are presented with a standard set of questionnaires and forms. This set includes an informed consent form, and a baseline questionnaire that asks detailed information about previous and current illnesses, medications (including OTC and herbal supplements or vitamins), family history of cancer, and lifestyle. In addition, dietary information is gathered using a well validated Food Frequency Questionnaire. The TCC collects biopsy tissue, medical records, a registration form, and a blood sample.

The following table summarizes data collected to-date:

Data Type	
Baseline questionnaire	68
Follow-up Questionnaire	86
FFQ	65
Blood sample	153
Urological Symptoms Questionnaire	50*
Pathology Reports	85
Frozen tissue sample	34

*Discontinued under revised protocol

Task 4: Randomization (Months 4-34)
There is no run-in period for this study. Subjects are randomized at the time of enrollment. Due to the short time subjects are required to participate in the study, randomization of new patients will continue throughout the study period.

Task 5: Follow-Up (Months 4-36)
Although the original statement of work calls for selenium supplementation and follow-up through the end of the grant period, we have limited supplementation and follow-up to the completion of prostate surgery in accordance with the revised study objectives. Under the revised study design, participants have their blood drawn and complete a follow-up questionnaire just prior to their prostate surgery. The follow-up questionnaire is designed to document pill compliance and possible adverse events.

Task 6: Laboratory Analyses (Months 3-30)
The following table describes the schedule for blood collection and analyses:

	Initial	Pre-Surgery
CMP	X	
Selenium	X	X
Lycopene	X	
Alpha Tocopherol (Vitamin E)	X	

We are continuing immunohistochemical tissue analysis for MIB-I, Bcl-2, and p53.

Task 7: Data Entry (Months 3-36)
All forms, questionnaires, and laboratory results are being entered into the database by the trained coordinators and laboratory assistants as they are received. Data are checked semi-annually during Quality Control reviews.

Task 8: Data Analyses and Report Writing (Months 28-36)
During the last months of the funding period, analyses of the collected data will be completed and reports and manuscripts for publication will be prepared and submitted.

KEY RESEARCH ACCOMPLISHMENTS

Analyses are being performed on both frozen and paraffin-embedded samples when both are available. This will enable us to analyze the comparability of assays performed with different forms of the same tissue for this and future studies.

REPORTABLE OUTCOMES

We have insufficient data at this time to report any preliminary outcomes with any confidence. We are re-evaluating our use of Bcl-2, and are inclined not to use it further. Although it may well predict PCa susceptibility, its expression is so uncommon in tumor tissue as to limit its usefulness in this research. In addition, we are continually re-evaluating the best assays to perform for this study based on the most recent scientific evidence and may very well substitute assays not initially envisioned, for example, cyclooxygenase-2. Since we submitted the original version of this proposal, additional research has focused on the importance of the cycloxygenase-2 system in prostate cancer. One of our collaborators-Dr. Koki- has shown a substantial increase in cycloxygenase-2 expression in prostate cancer. It is also known that cycloxygenase-2 is associated with decreased apoptosis, with increased proliferation, and with increased angiogenesis. In experiments in our laboratories, we have shown that in cell culture, addition of selenomethionine is associated with decreased cell growth, decreased cox-2 protein and mRNA expression, and decreased PGE-2 expression. There is additional external evidence from a breast cancer mouse model that selenium compounds decrease angiogenesis in vivo. These stated together lead us to strongly suspect that cycloxygenase-2 expression could be highly relevant to the impact of selenium on the risk of prostate cancer.

CONCLUSIONS

This innovative Phase II clinical trial, the *Chemoprevention Trial of Selenium and Prostate Cancer*, will provide new important information on biological endpoints in a population of ethnically diverse men with localized PCa prior to the initiation of other therapy. The effect of selenium supplementation on study participants who have undergone surgical resection of the prostate will provide insight into the possible effect of selenium supplementation on biomarkers for PCa and potential mechanisms of Se action. This research, critical in establishing the biological plausibility of selenium as a preventive agent for prostate cancer, can provide direct evidence for the effects of selenium on prostate tissue by examining this tissue before and after selenium supplementation.

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